



14/Declaration
1.132

Patent
Attorney's Docket No. 003300-763

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of)
John KENDRUP *et al.*) Group Art Unit: 1615
Application No.: 09/819,813) Examiner: Amy E. Pulliam
Filed: March 29, 2001) Confirmation No.: 1138
For: METHOD FOR PRODUCING A)
CONTROLLED-RELEASE PREPARATION)

DECLARATION UNDER 37 C.F.R. § 1.132 OF JOHN KENDRUP

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P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, John Kendrup, declare as follows:

- (1) I reside at Tegelbruksvagen 165, 238 39 Oxie, SWEDEN.
- (2) I have been employed by Amarin Development AB since 10 November 1995.
- (3) I am a Research Scientist and Doctorate student at the University of Lund.
- (4) I obtained a Bachelor's degree in chemical engineering and a Master's degree in Physical Chemistry from the University of Lund, as indicated on the attached Curriculum Vitae (Attachment A).
- (5) I am a listed inventor on the above-referenced application, which relates to a method for producing a controlled-release preparation.
- (6) I have read the Office Action dated January 27, 2003 (Paper No. 11) for the above-referenced application.
- (7) I provide herein evidence which supports the conclusion that the present invention is patentable over the reference (U.S. Patent No. 5,639,476 issued to Oshlack *et al.*,

hereinafter referred to as "Oshlack" or "the '476 patent") cited in the Office Action dated January 27, 2003.

INTRODUCTION

(8) The claims of the present application relate to methods of producing controlled release pharmaceutical preparations by preparing a drug containing solid core, suspending a pore-forming agent having a balanced solubility in an aqueous dispersion, coating the solid core with the suspension, and drying the coated tablet. The claims also relate to controlled release preparations comprising a solid core and a pore-forming agent having a balanced solubility in an aqueous dispersion.

Balanced Solubility

(9) "Balanced solubility" describes one important feature of the pore-formers used in the methods and preparations of the instant invention. A suitable solubility, or balanced solubility, is determined by three factors. First, during the manufacture of the pharmaceutical formulation, a coating dispersion is sprayed onto the active ingredient containing cores. This coating dispersion consists mainly of a dispersed water-insoluble polymer, a pore-former and water. In practice, the dispersion consists of about 85% (w/w) water, which leaves about 15% of solids. Thus, for example, 1 mL of a typical coating dispersion consists of 850 mg water, 100 mg pore-former, and 50 mg water-insoluble polymer (plasticizer included). The main portion of the pore-former should be suspended. Because of the suspension requirement, the maximum solubility of the pore-former is limited to approximately 10 mg/mL (*i.e.*, 90% of the pore-former is undissolved).

(10) The second factor governing balanced solubility involves the issue of keeping the particle-size of the pore-former unchanged. As shown in Table I, particle size greatly impacts the release rate of the active ingredient from the controlled release preparation. Several phenomenon can cause changes to particle size including (1) Ostwald ripening, (2) agglomeration between the pore-former particles, and (3) interactions between pore-former particles and the dispersed polymer particles. Ostwald ripening describes the observation that smaller particles dissolve faster than larger particles. Similarly, larger particles will grow on the behalf of the smaller particles. These observed phenomenon also prevent one from determining the maximum solubility for the pore-formers of the instant invention.

Lag-Time

(11) The third factor that determines the balanced solubility of the pore-formers is the lag-time. The preparation comprising the pore-formers should dissolve within a reasonable time after administration to the subject to avoid unnecessary delay in onset. The solubility of the pore-former has a strong influence on the lag-time observed after administration.

(12) The preparations of the instant invention, which comprise potassium hydrogen tartrate (*i.e.*, KHT) shown in Table I, have lag-times of about one hour. The one hour lag-time is approximately the amount of time needed for a preparation to begin the release of the drug. The concept of balanced solubility estimates that the solubility of the pore-formers in the water-based coating dispersion at the appropriate temperature should be in the order of 10 mg/mL to generally be undissolved in the coating dispersion, but sufficiently soluble in the gastrointestinal tract to permit time appropriate release of the active agent.

Coatings

(13) Coated pharmaceutical preparations have been known in the art for a long time. Coatings can be applied in single units or in multiple units. In terms of coatings for controlled release formulations, the major property of the coating other than strength is its permeability to water, drug and excipients. Zero coating permeability prevents any release of the active ingredients (assuming that the coating covers the entire preparation and does not break). Most polymers with good coating properties have permeabilities too low to be suitable for controlled release formulations. Incorporated pore-formers can increase the permeability of the coating. A known technique to increase the permeability of the coating is to add water-soluble compounds. Such water soluble compounds include sugars, triethyl citrate and hydroxypropylmethylcellulose. However, a draw back with using these water soluble pore-formers is the loss of coating strength. Consequently, the amount of these water-soluble compounds that can be added for their pore-forming properties is limited by the detrimental impact of the pore-formers on coating strength. In contrast, the pore-formers used in the claimed methods and preparations provide coating strength, as well as porosity and solubility which was not previously known or taught in the art.

**OSHLACK DOES NOT TEACH OR RENDER OBVIOUS THE CLAIMED
INVENTION**

(14) Oshlack does not teach or suggest pore-formers which have "balanced solubility", let alone teach the importance of balanced solubility pore-formers in preparing controlled release formulations. Oshlack lists a wide variety of substances which have virtually all kinds of solubilities. Oshlack does not discriminate between the compounds listed based on their solubility. The Office Action refers to col. 10, line 45 to col. 11, line 42 of the Oshlack reference which is provided below:

For example, the pore-formers may comprise one or more water-soluble hydrophilic polymers in order to modify the release characteristics of the formulation. Examples of suitable hydrophilic polymers include hydroxypropylmethylcellulose, cellulose ethers and protein-derived materials. Of these polymers, the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. Also, synthetic water-soluble polymers may be used, such as polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, polyethylene oxide, etc., water-soluble polydextrose, saccharides and polysaccharides, such as pullulan, dextran, sucrose, glucose, fructose, mannitol, lactose, mannose, galactose, sorbitol and the like. In *[sic]* certain preferred embodiments of the present invention, the hydrophilic polymer comprises hydroxypropylmethylcellulose.

Other examples of pore-formers include alkali metal salts such as **lithium carbonate**, sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium acetate, sodium citrate, and the like. The pore-forming solids may also be polymers which are soluble in the environment of use, such as Carbowaxes®, Carbopol®, and the like. The pore-formers embrace diols, polyols, polyhydric alcohols, polyalkylene glycols, polyglycols, poly(a-w)alkylenediols, and the like.

Semipermeable polymers may also be incorporated in the controlled release coating as a pore-former to change the release characteristics of the formulation. Such semipermeable polymers include, for example, cellulose acylates, acetates, and other semipermeable polymers such as those described in U.S. Pat. No. 4,285,987 (hereby incorporated by reference), as well as the selectively permeable polymers formed by the coprecipitation of a polycation and a polyanion as disclosed in U.S. Pat. Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006 and 3,546,142 (hereby incorporated by reference).

Other pore-formers which may be useful in the formulations of the present invention include starch, modified starch, and starch derivatives, gums, including but not limited to xanthan gum, alginic acid, other alginates,

bentonite, veegum, agar, guar, locust bean gum, gum arabic, quince psyllium, flax seed, okra gum, arabinoglactin, pectin, tragacanth, scleroglucan, dextran, amylose, amylopectin, dextrin, etc., cross-linked polyvinylpyrrolidone, ion-exchange resins, such as potassium polymethacrylate, carrageenan, kappa-carrageenan, lambdacarrageenan, gum karaya, biosynthetic gum, etc. Other pore-formers include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain, microporous materials such as bisphenol, a microporous poly(vinylchloride), microporous polyamides, microporous modacrylic copolymers, microporous styrene-acrylic and its copolymers, porous polysulfones, halogenated poly(vinylidene), polychloroethers, acetal polymers, polyesters prepared by esterification of a dicarboxylic acid or anhydride with an alkylene polyol, poly(alkylenesulfides), phenolics, polyesters, asymmetric porous polymers, cross-linked olefin polymers, hydrophilic microporous homopolymers, copolymers or interpolymers having a reduced bulk density, and other similar materials, poly(urethane), cross-linked chain-extended poly(urethane), poly(imides), poly(benzimidazoles), collodion, regenerated. [*sic*] proteins, semi-solid cross-linked poly(vinylpyrrolidone). (Emphasis added)

(15) It is clear from the above passages that the pore-formers cited by Oshlack are not discussed with regard to solubility. In fact, except for one pore-former cited by Oshlack (*i.e.*, lithium carbonate), all the remaining pore-formers have solubilities which are either too high or too low for use in the claimed preparations or methods of preparing the preparations. Moreover, Oshlack does not teach or suggest that the selection of pore-formers should be based on solubility, either in the above selected passages or anywhere in the '476 patent. Therefore, Oshlack does not teach or suggest the methods of preparing preparations using balanced solubility pore-formers as claimed in the instant invention.

(16) The only pore-former which potentially has a suitable solubility as needed for the claimed method is lithium carbonate (Oshlack at col. 10, line 62). However, an artisan of ordinary skill would not consider using lithium carbonate as a pore former, because pharmacologically, lithium carbonate is a potent active pharmaceutical ingredient (*i.e.*, categorized as an antimanic compound according to THE MERCK INDEX). Pore-formers should be pharmaceutical excipients, used to convert pharmaceutically active compounds into pharmaceutical dosage forms suitable for administration to patients, not pharmacologically active agents.

(17) As any reference must be viewed on what it teaches as a whole in view of what was known at the time, there is nothing in the Oshlack reference that would teach the skilled artisan the methods and preparations of the instant invention.

(18) Oshlack further does not teach or suggest the importance of the choice of coating to be used in combination with a specific pore-forming compound, especially pore-forming compounds with balanced solubility. Coated pharmaceutical preparations are known. With regard to controlled release coatings, the major property (other than strength) is the permeability of the coating to water, drug and excipients. For instance, zero permeability gives no release of the active ingredient(s) provided that the coating covers the entire preparation and does not break. Most polymers with good coating properties have permeabilities that are too low to be suitable for controlled release applications.

(19) Although pore-formers can increase the permeability of the coating, the main draw back with the use of pore-formers such as sugar, triethyl citrate and hydroxypropyl methylcellulose is the loss in coating strength. Consequently, the amount of the pore-former which can be added to a coating is limited by the detrimental impact of these pore-formers on coating strength. Oshlack does not suggest combinations of pore-former and coating compounds which are to be used to optimize coating strength and active ingredient release, let alone used in the claimed methods and formulations.

DISCUSSION OF THE DATA PROVIDED IN THE INSTANT APPLICATION

(20) As discussed in paragraphs 10-13 above, the type and particle size of the pore-forming agent used in the coating of the core is very important for the lag-time and the release rate from the preparation, factors which to a large extent determine the absorption of the active ingredient in the gastrointestinal tract. In the instant application, the examples demonstrate the impact of particle size of the pore-forming agent compared to results obtained when no pore-forming agent was used. Some of the results discussed in the Examples of the instant application are summarized in Table I below.

TABLE I

Properties of Coatings Prepared by Different Compositions with PVAc-Polymer

Pore-former	Amount released after 8 hours (%)	Strength of the Coating (N) ¹
60% (w/w) KHT ²	20	27
80% (w/w) KHT ²	93	20
KHT 8 μ m	62	- ³
KHT 14 μ m	37	- ³
No pore-former, normal weight gain	0	N/A ⁴
No pore-former, 1/4 weight gain	22	0 ⁵

(¹) The strength of the coating should be more than 5 N to withstand the forces in the gastrointestinal tract without breaking.

(²) Potassium hydrogen tartrate (KHT) has a balanced solubility according to the definition given in the instant application.

(³) Not performed.

(⁴) Not applicable.

(⁵) The coating burst during the dissolution test.

(21) The measurement of the strength of the coatings was performed as follows. The finished coated preparation was submerged into water for approximately 24 hours. During this period of time, the pore-former and the main part of the core dissolved. The remaining water-filled coating was then tested in the test apparatus from Mecmestin. In the test, the water-filled coating, which resembles a small balloon, was pressed between two plates at 1000 mm/min, and the maximum required forced was registered.

(22) From Table I, it can clearly be seen that without the pore-former the preparation fails. The failure is due to either the release of the active agent being too slow or the strength of the coating being too poor. It can also be seen that the particle size of the pore-former has a large impact on the release rate of the active agent. Furthermore, one can see that the release rate can be varied over a wide range merely by changing the amount of the pore-former, while still obtaining a coating with good mechanical strength. Thus, the values in Table I demonstrate that the amount and the particle size of the pore-former are important features of the invention.

(23) For comparison, experiments have been performed which demonstrate the differences between using pore-formers which do not have balanced solubility with

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pore-formers which have balanced solubility as discussed in paragraphs 21-23 above. The pore-formers tested were sucrose, lactose and Methocel E5, which all have the characteristics of being "highly soluble" in water and which will dissolve in the coating dispersion. The following coating experiments were performed with 60% (w/w) dissolved pore-former and 40% (w/w) dispersed PVAc-polymer as the aqueous coating dispersion. As can be seen from Table II, the pore-formers which dissolve (*i.e.*, those with high solubility such as sucrose, lactose and Methocel E5) fatally impacts the properties of the coating.

TABLE II

Pore-former	Amount released after 8 hours (%)	Strength of the coating (N) ¹	Coating Appearance
60% (w/w) sucrose	N/A ²	0 ⁴	Damaged
60% (w/w) lactose	N/A ²	0 ⁴	Damaged
60% (w/w)Methocel E5	100% after 2 hours	0 ³	Good

(1) The strength of the coating should be more than 5 N, to withstand the forces in the gastrointestinal tract without breaking.

(2) Not applicable.

(3) The coating disintegrated during the dissolution test.

(4) The coating was damaged during the coating process.

The above results clearly demonstrate that none of these pore-formers favorably compare with potassium hydrogen tartrate (KHT) as a suspended pore-former, shown in Table I. The pore formers of Table II all have solubilities too high to be used in the methods and formulations of the instant invention, which is distinguishable for its use as a balanced pore-former. Using a balanced solubility pore-former, such as those of the instant invention, allows preparation of a formulation with appropriate time release and good coating strength. Pore-formers with "high solubility" do not have these characteristics and therefore cannot be used for the claimed methods and formulations.

(24) The method according to the present invention, *i.e.* suspending the pore-former as particles with a balanced solubility, also makes it possible to control the size of the pores in the coating. As compared to other methods known in the art, the present method makes it possible to eliminate organic solvents to prepare these formulations yet still produce a coating with the desired properties (*i.e.*, a coating which has sufficient mechanical strength and which does not rupture in the patient after administration). The pores of the coating extend

continuously through the coating and can be made large enough to permit release of the active substance. The active substance is released through the water-filled pores, which form when the pore-form is dissolved, for example, in the gastrointestinal tract. The large continuous pores also allow convective flow of water when the preparation is exposed to pressure. This convective flow can relieve increased pressure caused by external pressure or by swelling of the preparation. In coatings with no pores (*i.e.*, semi-permeable polymers) or with small pores, pressure relief cannot occur and may lead to rupture of the formulation and premature and unwanted release of the active ingredient.

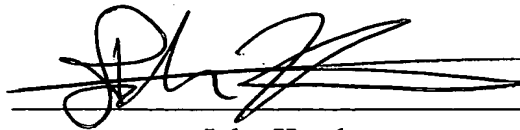
CONCLUSIONS

(25) Therefore, the coatings prepared using the pore-formers of the instant invention possess the desired properties of (1) good coating strength, (2) appropriate release of the active ingredient at a rate acceptable for active ingredient delivery to the patient, and (3) substantially decreased risk of rupture of the formulation due to pressure. None of these attributes are discussed in the Oshlack reference, nor are methods taught or suggested for overcoming these defects with regard to any pore-former, let alone with relation to the use of the pore-formers of the instant invention.

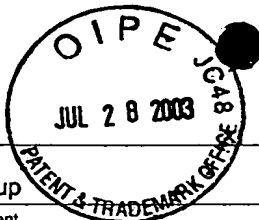
(26) I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of the application or any patent issuing thereon.

02 July 2003

Date



John Kendrup



CURRICULUM VITAE

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Date	Signature	Initials JKP
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QUALIFICATIONS *(in chronological order)*

Institution	Degree/Course	Period of study	Year completed
	Upper secondary school, technology	3 year	1990
Swedish Army	Military squad armour/shooting	10 months	1991
University of Lund	Chemical Engineer	80 p	1993
University of Lund	Fil mag Physical Chemistry	160 p	1998

PREVIOUS EMPLOYMENT *(in chronological order)*

Employer	Job title/Task	From	To
Apoteksbolaget	Laboratory Assistant trainee	920609	920717
Purac Industri AB	Engineer, trainee	930601	930730
Pharmacia AB	Technician, in Process	941101	951109
Gacell/Ethical/Amarin	Lab Engineer	951110	001231

PUBLICATIONS *(Author, title, journal)*

May be listed below or on a separate enclosure
